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Authors

Granger, Richard
Deadwyler, Sam
Davis, Mike
et al.

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Facilitation of Glutamate Receptors Reverses an Age-Associated Memory Impairment in Rats

RICHARD GRANGER, SAM DEADWYLER, MIKE DAVIS, BRIAN MOSKOVITZ,
MARKUS KESSLER, GARY ROGERS, AND GARY LYNCH

Center for the Neurobiology of Learning and Memory, University of California, Irvine, California, 92717 (R.G., M.D., B.M., M.K., G.L.); Departments of Physiology and Pharmacology, Wake Forest University, Winston-Salem, North Carolina 27153 (S.D.); and Cortex Pharmaceuticals, Inc., Irvine, California 92718 (G.R.)

KEY WORDS Glutamate receptors, Aging, Memory, Age-related memory impairment

ABSTRACT The accuracy of memory for recent events is reported to decay between young adulthood and middle age in humans (Crook et al., 1990; Crook and West, 1990; Thomas et al., 1977) due to impairments in acquisition and/or retention (Craik, 1977; Huppert and Kopelman, 1989). Effects of this kind are also found in comparisons of middle-aged (12–18 months) vs. young adult (3 months) rats in tests requiring retention of recently sampled spatial cues (Kadar et al., 1990a; Kadar et al., 1990b; Goudsmit et al., 1990; Weiss and Thompson, 1991). The causes of such changes in memory processing are unknown but might be expected to involve age-related losses in forebrain glutamate receptors (Bahr et al., 1992; Magnusson and Cotman, 1993; Wenk et al., 1991); these receptors mediate fast excitatory transmission in many brain regions and play an essential role in the production of long-term potentiation (LTP), a form of synaptic plasticity that has been implicated in memory encoding (Landfield and Lynch, 1977; Moore et al., 1993). In the present communication we report results indicating that a drug that enhances AMPA-type glutamate receptors acts centrally to selectively increase hippocampal spatial cell firing and improves both acquisition performance and memory retention in middle-aged rats to levels equivalent to those found in young adult animals.

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INTRODUCTION

AMPA-type glutamate receptors, the most numerous receptors in forebrain, mediate virtually all fast excitatory transmission in the brain. Synapses are lost with age in animals and in humans (Masliah et al., 1993) and glutamate receptors are selectively susceptible (Bahr et al., 1992; Magnusson and Cotman, 1993; Wenk et al., 1991); moreover, these losses occur over time courses comparable to that of age-related memory impairments. Taken together, the quantity, importance, and age-related loss of glutamate receptors suggests that their loss may be at least in part responsible for corresponding loss of memory function. If so, then selective enhancement of glutamatergic transmission should ameliorate these age-associated impairments. Previous studies have shown that the drugs from the Ampakine family, e.g., [1-(1,3-benzodioxol-5-ylcarbonyl)piperidine] (BDP) and derivatives, prolong the duration of AMPA-receptor-gated currents in excised patches (Arai et al., 1994) and increase the size and duration of fast,

excitatory synaptic responses in vitro and in vivo (Granger et al., 1993; Staubli et al., 1994b). These studies, and work with PET scans (Staubli et al., 1994a), also showed that BDP enters the brain within 1–3 min of intraperitoneal (i.p.) injection and is still present at 90 min. Pharmacokinetic analyses indicate that 30 mg/kg i.p. injections of the analogue compound BDP-12 result in mean blood plasma concentration of 55 μ M at 10 min and 30 μ M at 30 min, values which are near threshold for effects in vitro (Arai et al., unpublished data). This family of drugs has characteristics suggestive of agents suited to reverse age-associated memory impairment. It has been shown that middle-aged animals with no apparent neuropathology nonetheless exhibit reduced memory capabilities with respect to young animals (Kadar et al., 1990a; Goudsmit et al., 1990; Weiss and Thompson, 1991), providing an animal model

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of age-associated memory impairment in which to test the efficacy of Ampakines.

MATERIALS AND METHODS

Memory was tested using a conventional eight-arm radial maze paradigm. Acquisition performance and memory retention were measured in young (3 month) and middle-aged (14-month) male Long-Evans rats in daily sessions separated by either 5 h or 8 h delay intervals. During acquisition, rats were injected with either drug or control vehicle solution 20 min before being placed in the maze, in which access to three of the eight arms was blocked by barriers, and given 5 min to retrieve the five accessible (water) rewards. In the retention session, the three previously blocked arms were now open and baited, and the rewards omitted from the five arms that had been visited during the acquisition session; rats were permitted three attempts to obtain the three remaining rewards and were removed from the maze after each attempt.

Delayed match to sample was tested in an experimental chamber with two retractable levers on one wall and a nosepoke apparatus on the opposite wall. Each trial consisted of presentation of a sample, nosepoke, and match phase. In the sample phase, one of the bar press levers was extended into the chamber; after the rat pressed the lever, it was retracted and the rat crossed to the right side of the chamber to nosepoke, breaking a photobeam; then, in the match phase, both levers were extended into the chamber and the rat selected one of the levers to press. Drug was administered i.p. 10 min before a session. Hippocampal neurons were recorded simultaneously from a microwire recording array (Hampson et al., 1993b, 1994) implanted in CA1 and CA3 subfields of hippocampus. Single neurons were window-discriminated and isolated via a digital signal processor (DSP)-based "spike sorter" (Spectrum Scientific), time-stamped, and recorded in conjunction with behavioral and spatial position data on a laboratory computer. Spatial tracking consisted of 8-bit X and Y video tracking coordinates of red LEDs mounted above the animal's head.

RESULTS

Spatial cell firing

Figure 1 illustrates the effects of 30 mg/kg injections of BDP-12 on the firing of single hippocampal units recorded from freely moving animals actively engaged in a well-learned delayed match to sample task, chosen for its stereotypical repetitive movements that enable reliable recording over multiple behavioral trials. Hippocampal neurons were recorded from a microwire recording array (Hampson et al., 1993a,b, 1994) implanted in CA1 and CA3 subfields of hippocampus, during trial sessions beginning 10 minutes after an injection of drug or vehicle. Shown are the number of times each of four neurons fired in each 1.5 cm × 1.5 cm

location in the experimental chamber, with and without drug (Fig. 1a,d respectively), normalized by the total time the animal spent in that location and scaled to the maximum firing rate for that neuron (red, highest; blue, lowest firing rate). The adjacent trial-based histograms (b,c) show the time course of each neuron's firing relative to the three behavioral events comprising the match to sample task, averaged over all correct trials, for control and drug, respectively. It can be seen that neural activity for all four units increased in the presence of BDP-12, and that the firing patterns were distinct for each neuron. Results similar to these were obtained in four additional rats. These findings indicate that the drug has central action at a dose of 30 mg/kg i.p. Moreover, the drug strongly affects the spatiotemporal patterns of hippocampal neurons commonly associated with behaviorally relevant spatial learning. This naturally raises the question of what resulting behavioral changes might occur, especially in a spatial environment, at this dose.

Spatial maze learning

Memory was tested using a conventional eight-arm radial maze paradigm. Acquisition performance and memory retention were first measured for naive young (3 months, $n = 8$) and middle-aged (14 months, $n = 8$) rats all of whom had received only three days of acclimatization to the maze; these animals were then given months of subsequent experience in the maze and the experiment replicated in the now-experienced animals.

The protocol was constant throughout the experiment: there were two sessions (acquisition and retention) each day, initially separated by a 5-h delay for the naive animals and then by an 8-h delay when they were experienced. During the acquisition session, rats were injected with either drug (30 mg/kg BDP-12) or saline 20 min before being placed in the maze, in which access to three of the eight arms was blocked by barriers. The rats were given five minutes to retrieve the five accessible (water) rewards. After the intersession delay each rat was again placed into the maze for a retention session, in which the three previously blocked arms were now open and baited, and the rewards omitted from the five arms that had been visited during the acquisition session. The rats were permitted three attempts to obtain the three remaining water rewards, and were removed from the maze after each attempt.

In the first experiment, half (four) of the middle-aged rats received drug for three consecutive experimental days while the remainder received control injections, and then after 5 days of control-only injections for all animals, the groups were reversed so that the remaining four middle-aged rats received drug injections for three additional experimental days. Throughout the experiments, young animals received only control injections. Significant differences were found between the acquisition behaviors of the young versus middle-aged

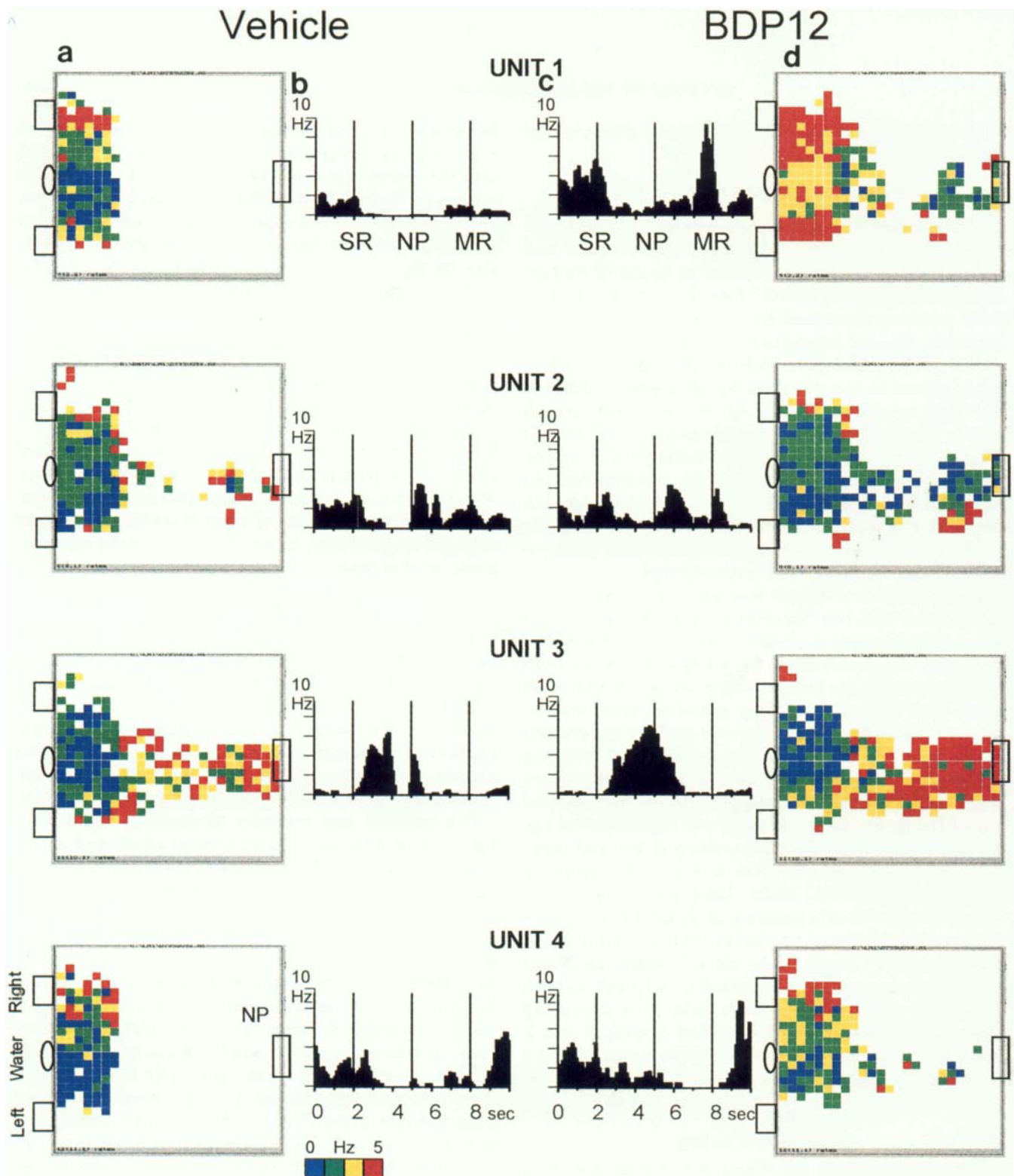


Fig. 1. Effects of BDP-12 on neural activity of four simultaneously recorded hippocampal neurons in a rat performing a spatial delayed match to sample task. In each trial, one of two bar-press levers was extended into the left side of the experimental chamber; after the rat pressed the lever (SR, sample response), the lever was retracted and the rat then crossed to the right side of the chamber to nosepoke (NP), breaking a photobeam; then both levers were extended into the chamber and the rat pressed the same one as before (MR, match response), to receive a water reward. Drug was administered i.p. 10 min before a session. Both spatial firing rate maps (a,d) and trial based histograms (b,c) are shown for rats receiving 30 mg/kg i.p. BDP-12 versus an equivalent injection of cyclodextrin vehicle. Spatial maps (a,d): Each large square represents the interior of the experimental chamber. Retractable levers and water reward trough were located at left; nosepoke apparatus is at right. Small colored squares indicate the number of times a neuron fired in each 1.5 cm \times 1.5 cm chamber location, normalized by the total time the animal spent in that location. Colors are scaled in four equal increments to the maximum firing rate

for that neuron (red, highest; blue, lowest firing rate). Single neurons were window-discriminated and isolated via a digital signal processor (DSP)-based "spike sorter" (Spectrum Scientific), time-stamped, and recorded in conjunction with behavioral and spatial position data on a laboratory computer. Spatial tracking consisted of 8-bit X and Y video tracking coordinates of red LEDs mounted above the animal's head. Histograms (b,c): The "trial-based" histograms show the time course of each neuron's firing relative to behavioral events for each of the three phases (sample response (SR), nosepoke (NP), and match response (MR)) comprising the match to sample task. Firing around SR and MR corresponds to the left side of the spatial map, whereas firing around NP corresponds to the right side of the spatial map (a, bottom). Neural activity from two seconds before SR to two seconds after MR were averaged for all correct trials and normalized by the number of trials contributing to each 100 msec time bin (Hampson et al., 1993b). Horizontal axis: one tick, 1 sec; vertical axis, maximum firing rate (Hz). Neural activity for each unit increased in the presence of the drug, with distinct firing patterns for each neuron.

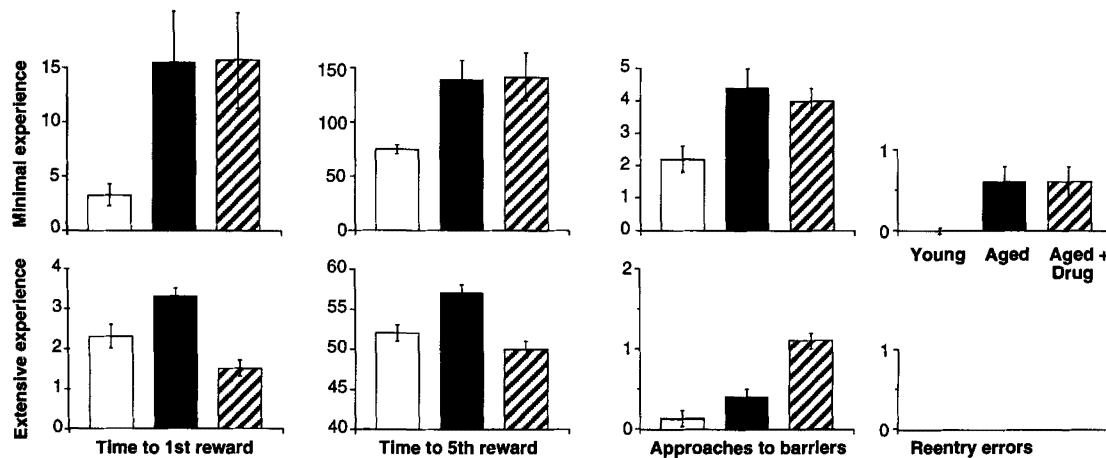


Fig. 2. Measures of behavior during morning acquisition sessions in the maze for young and middle-aged Long-Evans rats. Rats were given i.p. injections of either saline or BDP-12, placed in the maze 20 min later, and allowed 5 min to collect rewards. Three of the eight maze arms were blocked by barriers. Approaches to barriers and re-entries into arms already visited were counted, and the latencies to retrieve the first and all five rewards timed. Shown are means and standard errors for three groups of animals on 6 days of testing: young animals receiving saline (white), middle-aged animals receiving saline (black), and middle-aged animals receiving BDP-12 (striped). Top: Inexperienced animals. After three days of acclimatization to the maze, young (3 months; $n = 8$) and middle-aged (14 months; $n = 8$) animals were tested for 6 experimental days; half the aged animals received drug on 3 of these days and the other half of the aged animals received drug on the other three days. The values for the middle-aged animals were significantly different from those for the young animals

on all four measures ($P < .01$ for each measure) and were not detectably affected by drug administration. Bottom: Experienced animals. After 4 months of daily training, the experiment was repeated on the surviving animals (young now 7 months, $n = 8$; aged now 18 months, $n = 6$). Re-entry errors did not occur for any animal on any trial. On the remaining three acquisition performance measures, values for the middle-aged animals were still different from those for the young animals ($P < .02$ or less for each measure). Behavior was significantly more stereotyped and coefficients of variation for exploration times were decreased by more than a factor of 10 (from .74 to .03 for time to first reward, and from .14 to .001 for time to acquire all five rewards). BDP-12 significantly reduced the time to obtain 1st and 5th rewards ($P < .01$ for both measures; paired t -test) and increased the number of approaches to blocked arms ($P < .001$, paired t -test). (Note changes of y-axis scales.)

rats. In particular, the middle-aged animals took significantly longer than young animals to retrieve their first reward and to retrieve all five rewards, and made significantly more barrier approaches and re-entry errors ($P < .01$ for all measures; Fig. 2a). Animals receiving drug exhibited acquisition behaviors indistinguishable from their control scores.

On the retention test, administered 5 h after the acquisition session, the middle-aged animals on control injection days made significantly fewer correct responses than the young adults before their first re-entry error ($P < .002$) and significantly fewer total correct responses out of their three chances to obtain rewards ($P < .0005$). Memory retention of the middle-aged rats on drug injection days was significantly better than on control injection days ($P < .02$ for both measures, between animals on same days; Mann-Whitney U test; $P < .02$ for both measures, within animals across all experimental days; Wilcoxon signed-ranks test). The improvement was sufficiently large that the averaged memory scores for the middle-aged rats on drug days were virtually the same as those for the young animals (Fig. 3a).

Effects of experience

After extensive training, retention scores for the middle-aged animals rose to levels significantly above chance, so the delay interval between acquisition and retention sessions was lengthened from 5 to 8 h. The

above experiment was then repeated on the surviving animals [aged (now 18 months), $n = 6$; young (now 7 months), $n = 8$]. During the course of eight experimental days, half (three) of the aged animals received drug on days 1, 2, 5, and 6, while the other half received control injections; reciprocally, the other group of three aged animals received drug on days 3, 4, 7, and 8 while the first group received control injections. As before, the aged animals receiving control injections showed a marked retention deficit, an average of 54 ± 45 ($\bar{x} \pm \text{s.d.}$) % worse than young animals in number of correct responses before first error and an average of $35 \pm 18\%$ worse than young animals in total correct responses out of three attempts ($P < .05$ for both measures). Animals injected with drug exhibited significantly better retention on both measures ($P < .05$ for both measures), again rising to levels comparable to those of the young animals (Fig. 3b).

Aged animals without drug were still significantly slower than young animals, requiring one second longer to acquire their first reward ($P < .01$) and 5 sec longer to complete acquisition of all five rewards ($P < .002$). However, in contrast to the results obtained with the rats when they were relatively inexperienced, BDP-12 significantly reduced both latencies ($P < .001$) in the experienced middle-aged animals (Fig. 2b). The aged rats also exhibited a greater tendency to approach barri-

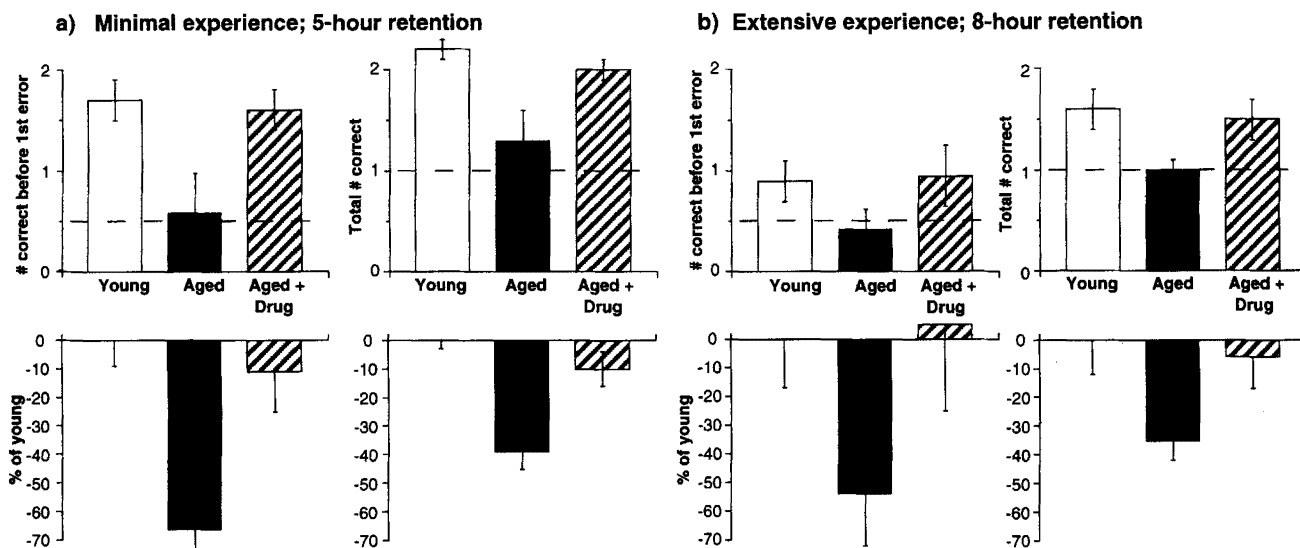


Fig. 3. Measures of memory during evening retention sessions for young and middle-aged rats. The three arms that had been blocked were now unblocked and baited; the five arms already visited during the acquisition session contained no reward. The animals were removed from the maze after each entry into a goal box, and given only three tries to retrieve the three water rewards. The number of successful retrievals of water rewards and the number of erroneous re-entries into unbaited arms were recorded for the middle-aged animals with and without BDP-12 and for the young animals with saline control injections. **a:** The top left graph shows the number of successful entries achieved before the first erroneous re-entry into an unbaited arm and the top right graph shows the total number of successful entries (out of the three attempts). The left and right bottom graphs show the same data but plotted as percentages of the values for the young animals. It can be seen that the young animals performed

significantly better on both of these measures than the middle-aged animals ($P < .002$ and $P < .005$ for the left and right measures, respectively, Mann-Whitney U). During the sessions when the aged animals received the drug, their performance on both measures was significantly improved ($P < .02$ for both measures, Wilcoxon signed-ranks test; $P < .004$, one-way paired t-test). The aged drug group was indistinguishable from the young group on both measures. **b:** Replication of results in part (a) on the same animals with an eight-hour delay between acquisition and retention sessions, after 4 months of daily experience in the maze (young = 7 mo., $n = 8$; aged = 18 mo., $n = 6$). Both the number of correct responses before first error and the total number of correct responses for aged animals was significantly different from that of young animals ($P < .05$, Mann-Whitney U, both measures), and the drug significantly reversed both age-related deficits ($P < .05$, Wilcoxon signed-ranks test, both measures).

ers during acquisition than did the younger animals ($P < .02$); interestingly, this tendency was significantly amplified with the drug ($P < .001$). Further analysis revealed that these approaches were performed after retrieval of all rewards, i.e., in further exploration during the acquisition session, once all rewards had been obtained. Experienced animals made no re-entry errors during acquisition, and the drug did not affect this.

Exploratory activity

The above findings raise the question of whether BDP-12 increases exploratory activity in middle-aged rats. Tests of this were made by counting rearings and center line crossings by rats placed in a familiar environment; as summarized in Table I, the drug produced a dose-dependent decrease in activity. These results are indistinguishable from those reported for young adult animals (Granger et al., 1993). Finally, the pattern of effects obtained with BDP-12 (faster performance, improved retention, modest reduction in exploration) has been fully replicated with a second and more potent analogue (data not shown).

DISCUSSION

The present study confirms earlier reports that a substantial deficit in recent memory for spatial loca-

tions emerges in rats between young adulthood and middle age (Kadar et al., 1990a,b; Goudsmit et al., 1990; Weiss and Thompson, 1991). The experiments also revealed that this age-associated retention deficit is not reversed by extensive training and is accompanied by significant changes in acquisition performance: middle-aged animals were significantly slower than young animals in exploring the maze and in obtaining rewards, and these age-related differences were not qualitatively changed even by extensive practice in the maze (Fig. 2). It seems reasonable to assume that the differences in acquisition behaviors contributed to the age-dependent changes in retention; for example, less efficient sampling patterns or repetition of extraneous behaviors by the middle-aged rats could affect their encoding of pertinent cues.

The drug BDP-12 caused selective changes in the firing of hippocampal spatial neurons. The increase in firing can be interpreted as a strengthening of an existing signal, but the changes in spatiotemporal cell firing suggest that additional or different spatial cues are being coded by these new firing patterns. Both effects would be expected to be accompanied by changes in spatial learning behavior. At the same dose that is effective in hippocampal units, BDP-12 improved reten-

TABLE I. Dose-dependent drug-induced reduction in spontaneous activity¹

	0 mg/kg	15 mg/kg	30 mg/kg	50 mg/kg	70 mg/kg
Rearing (number)	25.3 ± 8	20.9 ± 2.4	18.9 ± 1.6	16.3 ± 1.6	15.4 ± 2.2
Rearing (% reduction from baseline)	0.0 ± 4.3	-17.4 ± 9.6	-25.3 ± 6.9	-35.6 ± 6.6	-39.2 ± 8.9
Crossings (number)	19.3 ± 7	16.4 ± 1.5	14.4 ± 1.4	13.0 ± 1.1	10.8 ± 1.4
Crossings (% reduction from baseline)	0.0 ± 4.7	-14.8 ± 8.5	-25.2 ± 7.6	-32.5 ± 6.3	-43.9 ± 7.7

¹Middle-aged (avg. 15 mo.) rats (n = 10) were given injections of either saline or indicated dosages of BDP and 20 min later were placed in an activity box. Rearings and center-line crossings were counted for a 30 min period. Shown are means and standard errors for rearings and crossings for each dosage, and the same values expressed instead as a percentage reduction from the baseline (0 mg/kg) dose.

tion in middle-aged rats with minimal experience with the maze and again weeks later when the animals were performing at asymptotic levels. The compound also reversed age-related differences in acquisition behavior in the latter but not the former case. This differential effect strongly suggests that the enhancement of performance was not due to any stimulant-like properties of the drug, and indeed BDP-12 was found to cause a small but reliable decrease in scores in a standard test for behavioral arousal. Perhaps the simplest interpretation of this unusual constellation of effects is that facilitation of glutamatergic transmission enhances processing of complex but familiar cues (consistent with enlargement of spatial cell firing patterns), leading to more rapid performance in the radial maze and to accelerated habituation of exploratory behaviors. While such an action might also account for the observed improvement in retention, it should be noted that BDP analogues are reported to promote the induction of long-term potentiation in freely moving rats (Staubli et al., 1994a). In any event, the findings reported here suggest that centrally active facilitators of AMPA-type glutamate receptors may be useful as therapeutics for age-associated memory impairments.

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